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Signed A M Brewer

Dated 12 September 2000

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Patents Act 1977
(Rule 16)

-3 SEP 1999

The Patent Office

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effective

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference

PA9948

2. Patent application number
(The Patent Office will fill in this part)

9920758.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NYCOMED AMERSHAM PLC
Amersham Laboratories
White Lion Road
Amersham
Bucks HP7 9LL. GB

Patents ADP number *(if you know it)*

07395288001.

If the applicant is a corporate body, give the country/state of its incorporation

GB

4. Title of the invention

IMPROVED CONTAINER COMPOSITION FOR DIAGNOSTIC AGENTS

5. Name of your agent *(if you have one)*

Dr Anthony John ROLLINS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Nycomed Amersham plc
Amersham Laboratories
White Lion Road
Amersham
Bucks HP7 9LL. GB

Patents ADP number *(if you know it)*

05844139002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

NO

Patents Form 1/77

Improved Container Composition for Diagnostic Agents

Summary of the Invention

The present invention relates to improved containers for diagnostic agents, which are metal complexes useful as contrast agents for MRI or X-ray imaging, or hyperpolarised materials where the container has an internal coating of SiO_2. The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Field of the Invention

US 4385086 (1983) discloses the use of glass (and other materials) coated with highly oxidised silicon, to prevent the leaching of metal ions from the glass into the contents.

FR 2697014 A1 (1994) discloses the silica coating of the bottles, flasks, ampoules etc. for use with food or liquid pharmaceutical products to reduce leaching of metals into the liquid contents of the container.

DE 29609958 U1 discloses that glass containers having an internal coating of SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or diagnostic solutions.

JP 11-99192A discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as ^{201}Tl solution to the surface of the glass. No specific reference to radiopharmaceuticals which are metal complexes is made, and the main thrust of the invention is to a radiopharmaceutical vial having reversed text characters on the surface of the container. The silica coating of these vials is manufactured by the method described in JP 2815595 B which involves treating the glass surface with a silyl tetraisocyanate vapour in a carrier gas, followed by heating at high temperatures. JP 2815595 B also discloses that such a silica coating is useful to prevent leaching of impurities such as alkali from the glass into medical products.

US 5612103 discloses the use of coatings of deuterated polymers to inhibit the depolarisation of hyperpolarised gases within a container. WO 99/08941 discloses the use of glass vessels coated with a sol-gel, preferably an aluminosilicate glass, for the same purpose. WO 99/17304 discloses the use of a container made of a special glass having a low iron content for the same purpose.

Summary of the Invention

The present invention relates to silica-coated containers in combination with the following categories of diagnostic agents:

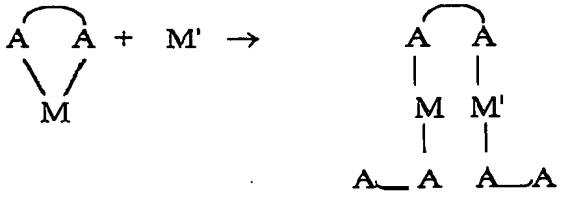
(i) lyophilised kits or liquid or solution formulations for the preparation of MRI contrast agents based on metal complexes of paramagnetic metal ions,

different and is not constrained to be 1, but is in the range of 1 to 8.
M'L is the metal complex impurity.

Step (i) can occur when the leached metal or metals (M') have greater affinity for the organic ligand (L) than the metal (M) of the product.

In addition to, or instead of equation (i), complexation (ii) may also occur. This leads to the presence of undesirable M'L impurities in the product ML.

When L is a multidentate ligand, such as a chelating agent the number of metal donor sites (A) per ligand (L) may be 2, 3, 4, 5, 6 or 8 typically. In that case, a process which is a special case of equation (i) above could occur as follows:

(iii)  where the free A donors can complex to further M/ M' atoms note: the curved lines represent the chain of atoms linking the A groups.

Leading to dimeric or oligomeric binuclear or polynuclear metal complexes involving both M and M'. The leached metal (M') may be less amenable to chelation by polydentate ligand (L), and hence favour such polynuclear species, even when M does not. This could result when the energetics are less favourable, e.g. M' is too small for two A groups to coordinate without undue steric interactions. In this way, a single M' atom could potentially generate a polynuclear or oligomeric species which comprises several M atoms. Clearly, the greater the denticity of the ligand L (i.e. the greater the number of A metal donor sites), the greater the potential complexity of the product.

The presence of such species may present impurity or manufacturing or irreproducibility problems due to vial-to-vial variations, or toxicity problems due to the impurity species or particulate problems when insoluble materials result. The latter would be a serious safety problem for products intended for human injection. Impurity species may also adversely affect product imaging performance by e.g. localising in undesirable background areas *in vivo* which adversely impact the image to be made.

In the light of the above, it can be seen that the influence of leachable metal ions (M'), can have effects which go far beyond simply the presence of metal ion impurities alone. This is important for metal complex contrast agent products, and is not recognised by JP 11-99192A which relates only to adsorption effects *via* an ion exchange mechanism for uncomplexed metal ions, i.e. ^{201}Tl as Tl^+ with the Na^+ and K^+ ions of the glass container walls.

For uncoated glass containers, the leaching of metal ions from the glass can be overcome by washing with dilute aqueous acid solutions (to remove relatively labile leachable metal ions), following by rinsing and (optionally) drying steps, before the container is loaded with product. The layer of SiO_2 suppresses any such leaching of metal ions (M'), and hence obviates the need for any such steps. This is particularly important for diagnostic products intended for human use, especially for human

All test solutions were measured by ICP for silicon, sodium, aluminium and boron, those cations considered to be most leachable from the vial surface. The results are given in Table 1.

Table 1

Test Number		Si	Na	Al	B
1		0.149	Nd	0.006	Nd
2		0.163	Nd	Nd	Nd
3	-70°C	0.167	Nd	0.00	0.00
	-20°C	0.193	0.005	0.002	0.002
	+20°C	0.193	0.009	0.005	0.003
	+40°C	0.236	0.006	0.002	0.002
4	bake	0.110	Nd	0.010	Nd
	X3	0.378	0.012	Nd	0.006
	gamma	0.102	0.003	Nd	Nd

Note: each table entry is the mean of 12 batch runs, each batch of 10 vials (i.e. 120 vials tested), expressed in $\mu g/cm^3$ of test solution.

Nd = not detected. Detection limits (in $\mu g/cm^3$):

Si – 0.003
Na – 0.004
Al – 0.004
B – 0.004

All of the results were satisfactory, particularly for the key cations sodium and aluminium, each of which had mean values of approximately 0.01μg per ml of test solution. These very low levels demonstrate the robustness of the silica coating under stress conditions.

There were no significant differences in the results obtained between vials from different proving runs. This demonstrates the reproducibility of the silica coating process.

Abstract

The present invention relates to improved containers for diagnostic agents, which are metal complex contrast agents for MRI or X-ray imaging, or hyperpolarised materials where the container has an internal coating of SiO_2. The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.